Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-126, 129-131 are pending in this application and are rejected on various grounds. Claims 119-123 have been amended with the recitation "native sequence," support for which is found at least on page 304, line 26 of the instant specification. The rejections to the presently pending claims are respectfully traversed.

Priority

Based on the discussions below, Applicants maintain their reliance on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, priority to which has been claimed in this application. Hence, the present application is entitled to at least the priority date of **June 23, 1999.**

Claim Rejections – 35 USC § 101 and §112, 1st paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-126 and 129-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention". Applicants respectfully disagree with and traverse these rejections.

The Examiner asserts that the invention lacks "specific" and "substantial" utility. The Examiner adds on page 4 of the Final Office action dated July 26, 2004 that "an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the prior art" and cites references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* for support. Regarding the Hanna and Mornin reference, the Examiner says on page 5, line 6 that their data is not persuasive because "it (is) difficult to extrapolate data from one protein, or its encoding gene, to another". Applicants respectfully traverse these rejections, for the reasons outlined below.

Utility Guidelines

In interpreting the utility requirement, in *Brenner v. Manson* [1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form." [2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy." [3]

Later, in *Nelson v. Bowler* [4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility." [5]

In *Cross v. Iizuka* [6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between." [7] The court perceived "No insurmountable

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility." [8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." [11], [12]

Compliance with 35 U.S.C. §101 is a question of fact. [13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. [14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

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[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons,* 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines") [15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial' utility."" [16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, [17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed 'native sequences' of the PRO1281 polypeptide of SEQ ID NO: 326.

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B) (1).

protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

On page 5, third paragraph of the Final Office action dated July 26, 2004, the Examiner asserts that,

> "(t)he fact that a particular **gene** is not amplified, in the absence of further supporting evidence from Applicants, does not provide a specific and substantial utility, or a well-established utility for that DNA. All it demonstrates is that that particular DNA is not involved in that particular cancer....Applicants have not demonstrated how the genomic DNA for PRO1281 fits into this equation...Any genomic DNA can be used for this purpose since all DNA levels will either increase, decrease, or remain the same," emphasis added.

Applicants strongly disagree. Applicants clearly presented supportive evidence and showed that the gene encoding for PRO1281 was significantly amplified, $2^{1.07}$ - $2^{1.15}$ fold, or 2.099 fold to 2.219-fold, in two out of two colon tumors studied (see Example 170 (page 554, Table 9C)). These values are considered significant based on the Declaration by Dr. Audrey Goddard (submitted herewith). Therefore the DNA encoding PRO1281 is clearly involved in colon cancer. The instant application is directed to native PRO1281 polypeptides. As discussed below, Applicants show that the art clearly shows that it is "more likely than not" for the corresponding polypeptide of an amplified DNA to also be overexpressed in the same tumor and have utility as a diagnostic markers in human colon cancers.

On page 4, line 18 of the Final Office action dated July 26, 2004, the Examiner asserts that the art supports that "an increase in nucleic acid copy number is not predictive of a similar association for protein" based on the teachings of prior art references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* Applicants respectfully traverse.

Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene" in 84% of the tumors examined.

While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. Similarly Konopka only addresses the *abl* gene, again not genes in general, and is therefore not an appropriate reference for making a *prima facie* case for lack of utility. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica and Konopka teach nothing of the correlation between gene amplification and polypeptide over-expression in general.

The Examiner adds that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels" (Page 4, line 25 of the Final Office Action). Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (see Figure 1) (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, Haynes shows that there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the Figure shows that the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." But, it is not a legal requirement to accurately predict protein levels from the evidence presented nor to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels, as discussed above. Moreover, in Figure 1 or Haynes, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Therefore, the Haynes data, in fact, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Thus, Applicants submit that the Examiner's rejection is based on a misunderstanding of the scientific data presented in Haynes *et al.*

Therefore, contrary to the Examiner's assertion, the cited art does not support the teaching that "nucleic acid copy number is not predictive of a similar association for protein" in general.

In fact, Pennica's, Konopka's and Haynes' teachings do not provide sufficient reasons to doubt the Applicants statements regarding PRO1281's utility as a marker to diagnose cancer.

In fact, the correct test for utility is whether it is "more likely than not" that, a positive correlation exists between proteins and nucleic acid levels. Based on the teachings of Ornoft, Pollack and Hyman (previously submitted) and the Haynes reference cited by the Examiner, a vast number of genes studied in these references indicated that "there was a general trend between increased protein expression and transcript levels," which meets the "more likely than not" standard and clearly shows that increased gene levels correlate well, in most genes, with increased expression of the protein.

Applicants further submit that, even if there were no correlation between gene amplification and increased mRNA/ protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Applicants' Response filed June 4, 2004) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Additional supporting evidence for such a utility is presented in a real-world example in an article by Hanna and Mornin (submitted with Applicants' Response filed June 4, 2004), which demonstrates a use for the breast cancer marker HER-2/neu. Hanna and Mornin teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH), as well as, the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Such testing is for the purpose of characterizing not the PRO1281 polypeptide, but the tumors in which the gene encoding PRO1281 is amplified. Therefore, the PRO1281 polypeptide is also useful in tumor

categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Based on the gene amplification data presented for PRO1281 in Example 170 of the specification, and all the submitted evidence, there is ample support for the Applicants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. One of skill in the art would therefore reasonably expect, based on: (a) the gene amplification data for the PRO1281 gene, (b) the supportive evidence in the Declarations submitted, and, (c) the supportive articles presented by the Applicants which were available in the art at the time of filing of the instant application, that the PRO1281 polypeptide is most likely, concomitantly, overexpressed in certain colon tumors, just like the PRO1281 gene, and is therefore useful as a tumor marker for certain colon cancers. Even in the event that the PRO1281 polypeptide were found not to be overexpressed in the colon tumors where the PRO1281 gene were amplified, (a position expressly not conceded to), the PRO1281 polypeptide is still useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

This opinion expressed by Dr. Ashkenazi in his Declaration, who is an expert in the field of Cancer biology and is a Director of Molecular Oncology at Genentech, Inc. is based on his factual findings and is supported by Hanna and Mornin's HER-2 gene/ neu protein study. Moreover, the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. [18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" [19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" [20] Applicants

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[18] *In re Rinehar,t* 531 F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

[20] *In re Alton*, supra.

also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which states that,

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Therefore, barring evidence to the contrary regarding the above statement in the Ashkenazi declaration, this rejection is improper under both the case law and the Utility guidelines.

Thus, Applicants submit that they have demonstrated utility for the PRO1281 polypeptide as a colon tumor marker based on gene amplification evidentiary data in the specification, and also based on supportive literature which was available to one of skill in the art at the time of filing. Moreover, the Patent Office has failed to meet its initial burden of proof that the Applicant's claims of utility are not "substantial" or "specific" based on the prior art papers presented by the Examiner, since they do not address general trends or genes "in general" and instead address isolated cases.

Applicants further submit that based on the claimed utility for PRO1281 polypeptides in the diagnosis of colon cancer, and the collective teachings in the specification, one of skill in the art would know exactly how to make and use the claimed polypeptide for the diagnosis of colon cancer. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility and enablement rejections should be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph-enablement

C. Claims 119-126 and 129-131 remain rejected under 35 U.S.C. 112, first paragraph since the skilled artisan would require undue experimentation to make and use the claimed invention.

The Examiner asserts that "simply providing a functional limitation in the claims with regard to the DNA would not allow the artisan to make (e.g. one which has at least 80% amino acid sequence identity to SEQ ID NO: 326) or use a protein which meets the limitations of the

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[21] Part IIB, 66 Fed. Reg. 1098 (2001).

claims...it would not be predictable to the artisan to (sic; how) either identify or make a protein encoded by DNA which is amplified in colon tumors".

Applicants respectfully traverse this rejection.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [22], [23] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue. [24] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue. [25], [26]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 5) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important" [27], [28]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount

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[22] M.P.E.P. §2164.01.

[23] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[24] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

[25] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

[26] M.P.E.P. §2164.06.

[27] M.P.E.P. §2164.08.

[28] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971).

of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[29]

The specification provides sufficient information to enable the claimed invention

First, Applicants respectfully maintain the position that Claims 119-126 and 129-131 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response.

Applicant respectfully submit that Claim 124 claims the full-length polypeptide of SEQ ID NO: 326, with or without its signal peptide sequence. Applicants have clearly provided the full-length sequence of SEQ ID NO: 326 for the PRO1281 polypeptide, and have identified its signal peptide sequence as comprising amino acid residues 1-15 (for example, see Example 102, page 485, line 35 and Figure 232). Thus one skilled in the art would easily know how to make the polypeptide, with or with out its signal peptide sequence. In addition, as mentioned above, the polynucleotide encoding PRO1281 was demonstrated to be amplified in colon tumors. Therefore, based on this information one skilled in the art would have known at the time of filing how to use the full-length PRO1281 polypeptide (SEQ ID NO: 326), with or without its signal peptide sequence, in the diagnosis and characterization of colon tumors. Accordingly, Claim 124 (and, as a consequence, those claims dependent from the same) meets the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants have also provided the native PRO1281 sequence SEQ ID NO: 326. The present application describes methods for identifying polynucleotides which are amplified in colon tumors in Example 170 which provides detailed protocols and assays for gene

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[29] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

amplification in colon tumors. By following the disclosure in the specification, one skilled in the art can easily test whether the gene encoding a variant native sequence PRO1281 polypeptide is amplified in colon tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 306, line 14 to page 308, line 6). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO1281 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making polypeptide variant sequences (see page 371, line 6 onwards) and methods of preparing the PRO polypeptides (see page 375, line 11 onwards). Thus, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO: 326. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

Therefore, Applicants further respectfully submit that one of skill in the art could readily test whether the polynucleotide encoding the variant native sequence polypeptide is amplified in colon tumors as set forth in the gene amplification assay (Example 170). The claims currently recite polypeptide sequences associated with a biological activity of the encoding polynucleotides. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." [30]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant native sequence PRO1281 polypeptides having at least 80% identity to SEQ ID NO: 326 wherein the polynucleotide

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[30] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v A.B. Fortia*, 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

encoding the polypeptide is amplified in colon or colon tumors, can be performed by techniques that were well known in the art at the priority date of this application, and that based on the teachings in the instant specification, the performance of such work does not require undue experimentation.

For the above-noted reasons, Applicants respectfully request the Examiner to reconsider and withdraw the enablement rejections under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 112, first paragraph-written description

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 112, first paragraph because, according to Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

The Examiner asserts that "(t)he general knowledge and level of skill in the art do not supplement the omitted description because specific guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus (i.e., of the protein, and not of their encoding DNA), and because the genus is highly variant, SEQ ID No: 326 is insufficient t describe the genus."

Applicants respectfully traverse this rejection to the pending claims.

The Legal standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[31, 32] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. The factual determination in a

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[31] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[32] See e.g., *Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [33, 34]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[35] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[36] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[37, 38]

The specification provides sufficient written description for the claimed invention

Applicants apologize for any inadvertent reference in the previous response to other SEQ ID Nos other than SEQ ID NO: 326.

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO1281 polypeptide of SEQ ID NO: 326, with or without its signal sequence. Further, as discussed above under the section of enablement, the specification clearly describes methods for the determination of percent identity between two amino acid sequences. (See page 306, line 14 to page 308, line 6). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the

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[33] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[34] *See also* M.P.E..P. §2163 II(A).

[35] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[36] *See also* M.P.E.P. §2141.03.

[37] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[38] S*ee also* M.P.E.P. §2141.03.

present invention, which is "specific guidance". The genus of the variant polypeptides thus have the common attributes of being "native sequences" whose encoding DNA give a positive in the gene amplification assay well described in Example 170 of the instant specification. Accordingly, one of skill in the art would know that Applicants could identify whether the variant PRO1281 native sequence fell within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making polypeptide variant sequences (see page 371, line 6 onwards) and methods of preparing the PRO polypeptides (see page 375, line 11 onwards).

Since the Law clearly says that "(t)he factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure," and the level of skill for one in the art is high, the skilled artisan would know that given the instant disclosure, Applicants were clearly in possession of the instantly claimed "native" variant polypeptides and their encoding nucleic acids that were tested in the gene amplification assay at the time of filing.

Therefore, Applicants respectfully maintain that Claims 119-126 and 129-131 satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Hence, Applicants submit that this rejection should be withdrawn.

Claim Rejections - 35 USC § 102

Claims 119-126 and 129-131 were rejected under 35 U.S.C. §102(b) as being anticipated by Baker *et al.* (WO99/63088) published December 1999.

As discussed above, Applicants have presented reasons why the instant application has patenatable utility. Applicants submit that, for the same reasons, the disclosure in U.S. Provisional Application 60/141037, filed **June 23, 1999** also has utility. Applicants have also made a proper assertion of priority based on U.S. Provisional Application 60/141037 and believe that they are entitled to this effective filing date. Accordingly, Applicants submit that Baker *et al.* is not prior art and hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C25). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: July 22, 2005

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